

**IN THE SPECIFICATION:**

Please insert the following paragraphs for the corresponding paragraphs in the specification:

Paragraph bridging pages 5 and 6

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b1  
-- In view of the circumstances described above, the present inventors have made extensive investigations to develop tablets of fast disintegration type and found that, when a pharmacologically active ingredient is subjected to surface modification with a surface modifying base material such as light silicic anhydride, etc., the surface-modified powders comprising a pharmacologically active ingredient with a good flowability can be obtained. The inventors have further found that blending of the surface-modified powders comprising a pharmacologically active ingredient with a disintegrant such as ~~partially alphanized~~ partly pregelatinized starch, crospovidone, etc. followed by direct tableting provides fast or rapidly disintegrating tablets that maintain an adequate hardness and are yet rapidly disintegrated and dissolved in the oral cavity without resort to complex production procedures such as heating, melting, dissolving, freezing, etc.; these complex procedures are usually required for conventional production steps. Based on the above findings, the present invention has been accomplished. --

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2<sup>nd</sup> whole paragraph on page 17

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b2  
-- Specific examples of the disintegrants used in the present invention include ~~partially alphanized~~ partly pregelatinized starch, crospovidone (Polyplasdone), crystalline cellulose-carmellose sodium, low substituted hydroxyl-propyl cellulose, corn starch, potato and other starches, carmellose, carmellose calcium, carmellose sodium, croscarmellose sodium, carboxymethylstarch sodium, etc. Among them, ~~partially alphanized~~ partly pregelatinized starch and crospovidone are particularly preferred.--

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Example 5, first full paragraph bridging pages 28 and 29

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-- A high speed agitation granulator (Laboratory Matrix LMA10 , manufactured by Nara Machinery Co., Ltd.) was charged with potassium gluconate and light silicic anhydride in the respective amounts indicated in TABLE 6 below. Surface modification was performed for 15

b3  
cont

minutes (conditions for the surface modification: main impeller of 300 rpm, granulation impeller of 1,500 rpm). Next, the whole amount of the pharmacologically active ingredient-comprising surface-modified powders of the present invention obtained above were taken out of the granulator. The remaining components given in TABLE 5 below, i.e., ~~partially alphanized~~ partly pregelatinized starch, glucono delta lactone, erythritol, crystalline cellulose and magnesium stearate were added to the powders, followed by mixing with a V-10 blender (manufactured by Tokujū Corporation) for 5 minutes. The mixture was then tableted with a pestle for odd-shaped tablets (16 mm X 7 mm) using a fully automated rotary tableting machine (manufactured by Hata Iron Works). Thus, the fast disintegrating tablets of the present invention were produced. Flavorings, sweeteners and so on may be incorporated to improve taste. --

Table 5 on page 29 and Example 6 on page 29-30.

TABLE 5

Formulation

<u>Component</u>	<u>Amount Added (unit: g)</u>
Potassium gluconate	500
Light silicic anhydride	5
<del>partially alphanized</del> <u>Partly pregelatinized</u> starch	215
Glucono delta lactone	12
Erythritol	50
Crystalline cellulose	100
Magnesium stearate	18
Total	900

b4

EXAMPLE 6

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vent

A high speed agitation granulator (Laboratory Matrix LMA10, manufactured by Nara Machinery Co., Ltd.) was charged with potassium gluconate and light silicic anhydride in the respective amounts indicated in TABLE 6 below. Surface modification was performed for 15 minutes (conditions for the surface modification: main impeller of 300 rpm, granulation impeller of 1,500 rpm. Next, the whole amount of the pharmacologically active ingredient-comprising surface-modified powders of the present invention obtained above were taken out of the granulator. The remaining components given in TABLE 6 below, i.e., crospovidone, glucono delta lactone, crystalline cellulose and magnesium stearate were added to the powders, followed by mixing with a V-10 blender (manufactured by Tokuju Corporation) for 5 minutes. The mixture was then tableted with a pestle for odd-shaped tablets (19 mm x 8 mm) using a fully automated rotary tableting machine (manufactured by Hata Iron Works). Thus, the fast disintegrating tablets of the present invention were produced. Flavorings, sweeteners and so on may be incorporated to improve taste.

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Example 7 on pages 30-31 followed by Table 7 and Example 8 on pages 31-33.

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#### EXAMPLE 7

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A high speed agitation granulator (Verticval Granulator FM-VG-01, manufactured by Powrex) was charged with bupranolol hydrochloride and lactose G. After blending with a main impeller and a granulation impeller, both at 500 rpm for 1 minute, 2 wt% of light silicic anhydride was added and surface modification was conducted for 10 minutes under the same conditions. The remaining components given in TABLE 7 below, i.e., ~~partially alphanized~~ partly pregelatinized starch and magnesium stearate were added to the powders, followed by blending a Transparent Micro V-Mixer (manufactured by Tsutsui Scientific Instruments Co., Ltd.) for 15 minutes. The mixture was then tableted with a flat-faced beveled edged pestle of 8.5 mm in diameter using a fully automated rotary tableting machine (manufactured by Hata Iron Works). Thus, the fast disintegrating tablets of the present invention were produced. Flavorings, sweeteners and so on may be incorporated to improve taste. --

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Table 7 on page 31 followed by Example 8 bridging pages 31 and 32

TABLE 7

Formulation

<u>Component</u>	<u>Amount Added (unit: g)</u>
Bupranolol hydrochloride	10
Lactose G	107.6
Light silicic anhydride	2.4
<del>partially alphanized</del> <u>Partly pregelatinized</u> starch	89.2
Magnesium stearate	0.8
Total	210

EXAMPLE 8

b6  
A high speed agitation granulator (Vertical Granulator FM-VG-01, manufactured by Powrex) was charged with glycopyrronium bromide and lactose (manufactured by Freund Industrial Co., Ltd., trade name: DAI-LACTOSE S). After blending with a main impeller and a granulation impeller, both at 500 rpm, for 1 minute, 1 wt% of light silicic anhydride was added and surface modification was conducted for 15 minutes under the same conditions. The remaining components shown in TABLE 8 below, i.e., crystalline cellulose, ~~partially alphanized~~ partly pregelatinized starch, erythritol and magnesium stearate were added to the powders, followed by blending a Transparent Micro V-Mixer (manufactured by Tsutsui Scientific Instruments Co., Ltd.) for 15 minutes. The mixture was then tableted with a pestle of 8.5 mm in diameter and 6.5R using a fully automated rotary tableting machine (manufactured by Hata Iron Works). Thus, the fast disintegrating tablets of the present invention were produced. Flavorings, sweeteners and so on may be incorporated to improve taste. --

Table 8 on page 33

TABLE 8

Formulation

<u>Component</u>	<u>Amount Added (unit: g)</u>
Glycopyrronium bromide	1
Lactose	99
Light silicic anhydride	1
Crystalline cellulose	30
<u>Partly pregelatinized</u> <del>partially alphanized</del>	100
starch	
Erythritol	16.5
Magnesium stearate	2.5
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Total	250

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Last paragraph on page 34

68 -- 4) The remaining components shown in TABLE 9 below, i.e., citric acid, ~~partially alphanized~~ partly pregelatinized starch, lactose, crystalline cellulose and magnesium stearate were added to the respective three pharmacologically active ingredient-comprising surface-modified powders, followed by blending a V-10 blender (manufactured by Tokuju Corporation) for 5 minutes. Each mixture was then tableted with a pestle of 10 mm in diameter and 7.5 mmR using a fully automated rotary tableting machine (manufactured by Hata Iron Works). Thus, the fast disintegrating tablets of the present invention were produced. Flavorings, sweeteners and so on may be incorporated to improve taste. --

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TABLE 9

Formulation

<u>Component</u>	<u>Amount Added (unit: g)</u>
Ibuprofen	75
Acetaminophen	150
Anhydrous caffeine	60
Light silicic anhydride	5.7
Citric acid	20
<del>partially alphanized</del> <u>Partly pregelatinized</u> starch	232.3
Lactose	100
Crystalline cellulose	50
Magnesium stearate	7
Total	700

69 TEST EXAMPLE 1

b9  
cont

In order to explain the effects achieved by the present invention in more detail, tablet characteristics were determined with the fast disintegrating tablets of the invention obtained in EXAMPLES and commercial products, and comparison was made between the tablets of the invention and the commercial products. The results are shown in TABLES 10 and 11. It is understood by comparing TABLES 10 and 11 that the fast disintegrating tablets obtained in the present invention are excellent in disintegratability and yet maintain a suitable strength. It is also confirmed that ~~partially-alphanized~~ partly pregelatinized starch and crospovidone were most suitable as the disintegrant.

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Paragraph bridging pages 39 and 40 and Table 12

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-- Thereafter, the whole amount of the pharmacologically active ingredient-comprising surface-modified powders of the present invention obtained above were taken out of the granulator. The remaining components given in TABLE 12 below, i.e., citric acid (manufactured by Wako Pure Chemical Industries Ltd.), ~~partially-alphanized~~ partly pregelatinized starch (manufactured by Asahikasei Corporation), crystalline cellulose (manufactured by Asahikasei Corporation, CEOLUS), talc (manufactured by Shokozan Mining Co., Ltd.) and magnesium stearate (manufactured by Kyodo Yakuhin K.K.) were added to the powders, followed by mixing with a V-10 blender (manufactured by Tokuju Corporation) for 5 minutes. By tableting the mixture with a pestle of 10 mm in diameter having flat-faced beveled edges using a tableting machine, the tableting problem was eliminated. Thus, the fast disintegrating tablets of the present invention were produced. The results indicate that by the multilayered surface modifying procedures, there could be obtained the fast disintegrating tablets available for low melting or strongly sticky drugs, irrespective of the shape of a pestle.

b10

TABLE 12

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Formulation

<u>Component</u>	<u>Amount Added (unit: g)</u>
Ibuprofen	800
Light silicic anhydride	8
Titanium oxide	24
Citric acid	136

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<del>partially alphanized</del> <u>Partly pregelatinized</u>	956
starch	
Crystalline cellulose	380
Magnesium stearate	48
Talc	48

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Total	2400
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Paragraph bridging pages 42-43 followed by Table 13

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-- Then, the whole amount of the pharmacologically active ingredient-comprising surface-modified powders of the present invention obtained above were taken out of the granulator. The remaining components given in TABLE 13 . below, namely, citric acid (manufactured by Wako Pure Chemical Industries Ltd.), ~~partially alphanized~~ partly pregelatinized starch (manufactured by Asahikasei Corporation), crystalline cellulose (manufactured by Asahikasei Corporation, CEOLUS), talc (manufactured by Shokozan Mining Co., Ltd. ), erythritol (manufactured by Nikken Chemical Industry Co., Ltd.), a flavoring agent (manufactured by . Ogawa Perfumery Co., Ltd.) and magnesium stearate (manufactured by Kyodo Yakuin K.K.) were added to the powders, followed by blending with a V-10 blender (manufactured by Tokuju Corporation) for 5 minutes. Any tableting problem that might be caused by tableting the blend with a pestle of 10 mm in diameter having flat-faced beveled edges using a tableting machine was not noted. Moreover, the thus produced fast disintegrating tablets of the present invention were improved on the stinging taste. The results indicate that by the multilayered surface modifying technique, the fast disintegrating tablets were found to be available for improving the taste of drugs having a bitter or stinging taste. --



TABLE 13

Formulation

<u>Component</u>	<u>Amount Added (unit: g)</u>
Ibuprofen	400
Light silicic anhydride	4
Titanium oxide	4
Finely divided erythritol	12
Citric acid	40
Erythritol	400
<del>partially-alphanized</del> <u>Partly pregelatinized</u> starch	480
Crystalline cellulose	1000
Flavoring agent (orange)	12
Magnesium stearate	24
Talc	24
Total	2400

Paragraph bridging pages 44-45 followed by Table 14

-- Next, the whole amount of the pharmacologically active ingredient-comprising surface-modified powders of the present invention obtained above were taken out of the granulator. The remaining components given in TABLE 14 below, namely, citric acid (manufactured by Wako Pure Chemical Industries Ltd.), ~~partially-alphanized~~ partly pregelatinized starch (manufactured by Asahikasei Corporation), crystalline cellulose (manufactured by Asahikasei Corporation, CEOLUS), talc (manufactured by Shokozan Mining Co., Ltd.), erythritol (manufactured by Nikken Chemical Industry Co., Ltd.), a flavoring agent (manufactured by Ogawa Perfumery Co., Ltd.) and magnesium stearate (manufactured by Kyodo Yakuin K.K.) were added to the powders, followed by blending with a V-10 blender (manufactured by Tokuju Corporation) for 5 minutes. The blend was tableted with a pestle of 10 mm in diameter having flat-faced beveled

edges using a tableting machine but no tableting problem was noted. Moreover, the thus produced fast disintegrating tablets of the present invention had a quality equivalent to those obtained in EXAMPLE 11 in terms of improvement in the stinging taste. The results indicate that by the multilayered surface modifying technique, the fast disintegrating tablets were found to be available not only for low melting or strongly sticky drugs but also for improving the taste of drugs having a bitter or stinging taste. It was confirmed that even if the order of adding the surface modifiers is changed, the tablet preparations can be obtained with an equivalent quality.

TABLE 14

Formulation

<u>Component</u>	<u>Amount Added (unit: g)</u>
Ibuprofen	400
Titanium oxide	4
Finely divided erythritol	12
Light silicic anhydride	4
Citric acid	40
Erythritol	400
<del>partially alphanized</del> <u>Partly pregelatinized</u>	480
starch	
Crystalline cellulose	1000
Flavoring agent (orange)	12
Magnesium stearate	24
Talc	24
Total	2400

Paragraph bridging pages 46-47 followed by Table 15 on page 48

-- Next, the whole amount of the pharmacologically active ingredient-comprising surface-modified powders of the present invention obtained above were taken out of the granulator. The

remaining components given in TABLE 15 below, namely, citric acid (manufactured by Wako Pure Chemical Industries Ltd.), ~~partially alphanized~~ partly pregelatinized starch (manufactured by Asahikasei Corporation), crystalline cellulose (manufactured by Asahikasei Corporation, CEOLUS), talc (manufactured by Shokozan Mining Co., Ltd.), erythritol (manufactured by Nikken Chemical Industry Co., Ltd.), a flavoring agent (manufactured by Ogawa Perfumery Co., Ltd.) and magnesium stearate (manufactured by Kyodo Yakuin K.K.) were added to the powders, followed by blending with a V-10 blender (manufactured by Tokuju Corporation) for 5 minutes. The blend was tableted with a pestle of 10 mm in diameter having flat-faced beveled edges using a tableting machine but no tableting problem was noted. The thus produced fast disintegrating tablets had a quality comparable to those obtained in EXAMPLE 12, indicating that trehalose is likewise available for the multilayered surface modification technique.

TABLE 15

Formulation

<u>Component</u>	<u>Amount Added (unit: g)</u>
Ibuprofen	400
Titanium oxide	4
Finely divided trehalose	12
Light silicic anhydride	4
Citric acid	40
Erythritol	400
<del>partially alphanized</del> <u>Partly pregelatinized</u>	480
starch	
Crystalline cellulose	1000
Flavoring agent (orange)	12
Magnesium stearate	24
Talc	24
Total	2400